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CLARK & ELBING LLP			SISSON, BRADLEY L	
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

<b>Office Action Summary</b>	<b>Application No.</b> 10/070,297	<b>Applicant(s)</b> TOCQUE ET AL.
	<b>Examiner</b> Bradley L. Sisson	<b>Art Unit</b> 1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If no period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED. (35 U.S.C. § 133).

Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

1) Responsive to communication(s) filed on 20 March 2008 & 28 April 2008.

2a) This action is FINAL.      2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

4) Claim(s) 27,30-33,44 and 47-53 is/are pending in the application.

4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.

5) Claim(s) \_\_\_\_\_ is/are allowed.

6) Claim(s) 27,30-33,44 and 47-53 is/are rejected.

7) Claim(s) \_\_\_\_\_ is/are objected to.

8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All    b) Some \* c) None of:  
 1. Certified copies of the priority documents have been received.  
 2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

1) Notice of References Cited (PTO-892)  
 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)  
 3) Information Disclosure Statement(s) (PTO/SB/08)  
Paper No(s)/Mail Date 5/5/2008

4) Interview Summary (PTO-413)  
Paper No(s)/Mail Date \_\_\_\_\_

5) Notice of Informal Patent Application  
 6) Other: \_\_\_\_\_

**DETAILED ACTION**

***Priority***

1. Acknowledgment is made of applicant's claim for foreign priority based on an application filed in France on 05 September 2000. It is noted, however, that applicant has not filed a certified copy of the PCT/FR00/02439 application as required by 35 U.S.C. 119(b).

***Claim Rejections - 35 USC § 112***

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 27, 30-33, 44, and 47-53 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 27 and 48 are the only independent claims pending. Claim 27 is deemed representative and for convenience, is reproduced below.

27. (Currently Amended) A method for the remote detection *in vitro* of the presence of a given, predefined pathological condition associated with a deregulation in a cell signaling pathway in a human subject, wherein said given, predefined pathological condition is a pathological condition that causes disease in a tissue distinct from blood cells of said human subject, said method comprising comprises:

- (i) providing a sample of blood cells from the subject, wherein said blood cells comprise lymphocytes, macrophages, monocytes or dendritic cells,
- (ii) preparing nucleic acid molecules from the sample of step (i), and
- (iii) obtaining a hybridization profile by hybridizing all or part of the nucleic acid molecules from step (ii) to so-prepared with at least one nucleic acid library comprising a plurality of nucleic acid molecules having an ordered arrangement on a support to obtain a first hybridization profile, wherein
  - (a) said plurality of nucleic acid molecules are specific for differentially spliced ribonucleic acid molecules (RNAs) expressed in blood cells from human subjects known to have having the given, predefined pathological condition, wherein  
(b)(a) expression of the presence of said differentially spliced RNAs being is

characteristic of said the given, predefined pathological condition, and

(c)(b) said blood cells from human subjects known to have said having the given, predefined pathological condition comprising comprise lymphocytes, macrophages, monocytes, or dendritic cells, and wherein

(c) the pathological condition affects a tissue distinct from said blood cells;

(iv) correlating the first hybridization profile with a second hybridization profile obtained by hybridizing nucleic acid molecules from blood cells of a subject known to have said given, predefined pathological condition to said nucleic acid library, thereby indicating wherein the hybridization profile indicates the presence of said given, predefined pathological condition in said subject.

4. For purposes of examination, the claims have been construed as encompassing a nucleic acid library that can comprise an infinite number of nucleic acids, all of which are bound in an ordered arrangement to a solid support, and which correspond to the “differentially spliced ribonucleic acid molecules (RNAs) expressed in nucleated blood cells from human subjects known to have [a] given, predefined pathological condition.”

5. A review of the disclosure fails to find where applicant has described any nucleic acid, much less a nucleic acid that corresponds to any “differentially spliced ribonucleic acid molecules (RNAs) expressed in nucleated blood cells from human subjects known to have [a] given, predefined pathological condition.”

6. A review of the specification does find at page 28 the following forward-looking statements as to how the invention can be practiced.

Nucleotide probes or PCR primers derived from these tumor-specific cDNAs can be used to screen for the expression, in human tumor biopsies, of the identified splicing forms and/or the RNAs whose quantities are altered in this model.

Similarly, the probes identified in the blood of animals at different stages of tumor development can also be used to detect signatures common to blood samples from cancer patients.

In a strategy which uses the cDNA banks obtained according to the aforementioned processes of the invention, a total probe prepared from blood samples from cancer patients can also be used to screen for signatures common to the different banks established from murine models at different stages of tumor progression, on the one hand, and from biopsies of different human tumors on the other hand. These hybridizations are carried out according to methods familiar to those skilled in the art (in particular, consult the hybridization conditions set forth in application No. PCT/FR99/00647).

#### RESEARCH FOR PREDICTIVE DIAGNOSIS IN MAN

The methods described in this section can be implemented by using either the quantitative or the qualitative analytical methods described above. Nonetheless, the invention favors the use and research of markers linked to qualitative alterations in gene expression, due to the aforementioned advantages.

7. While applicant urges "the use and research of markers," the specification has not been found to disclose any one of the markers.
8. Acknowledgement is made of where at page 12, bridging to page 13, of the specification does disclose using labeled oligonucleotide that correspond to cDNA when conducting Serial Analysis of Gene Expression (SAGE). In this instance, the probes are to be 10 nucleotides in length. It is noted that there are  $4^{10}$ , or 1,048,576 possible 10-mers. The specification has not identified which of these probes are useful in the claimed method.
9. On 19 May 2006 a declaration under 37 CFR 1.132 by Fabien Schweighoffer, a co-inventor named in the instant application, was filed. The declaration provides statements as to

identifying specific splicing markers in the early stage of BSE in blood samples of 5 experimentally infected cattle and 4 matching control animals. The declaration also discloses the production of a microarray; however, the declaration does not identify any nucleotide sequence for any nucleic acid bound to the support. It is further noted that the declaration does not teach the detection of any given predefined pathological condition in humans, as the claims are now limited. Further, the specification does not identify any controls, positive or negative, which are to be included inn the assay (limitations of claims 51 and 53).

10. In accordance with new claims 50 and 52, the method is to be practiced with RNA from lymphocytes, macrophages, monocytes or dendritic cells. The specification does not describe how any one, much less each of the different cell types are to be specifically isolated, and the RNA from same be isolated and used to detect any given, predefined pathological condition.

11. In accordance with claim 31, one is to amplify the nucleic acids; however, the specification is silent as to what primer(s) are to be used so to amplify the target nucleic acid sequence. Indeed, the specification has not identified any target sequence in such terms that any primer could be readily identified.

12. For the above reasons, and in the absence of convincing evidence to the contrary, claims 27, 30-33, 44, and 47-53 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

13. Claims 27, 30-33, 44, and 47-53 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which

was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As set forth in *Enzo Biochem Inc., v. Calgene, Inc.* (CAFC, 1999) 52 USPQ2d at 1135, bridging to 1136:

To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.' " *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997) (quoting *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)). Whether claims are sufficiently enabled by a disclosure in a specification is determined as of the date that the patent application was first filed, see *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986).... We have held that a patent specification complies with the statute even if a "reasonable" amount of routine experimentation is required in order to practice a claimed invention, but that such experimentation must not be "undue." See, e.g., *Wands*, 858 F.2d at 736-37, 8 USPQ2d at 1404 ("Enablement is not precluded by the necessity for some experimentation . . . However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.'") (footnotes, citations, and internal quotation marks omitted). In *In re Wands*, we set forth a number of factors which a court may consider in determining whether a disclosure would require undue experimentation. These factors were set forth as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *Id.* at 737, 8 USPQ2d at 1404. We have also noted that all of the factors need not be reviewed when determining whether a disclosure is enabling. See *Amgen, Inc. v. Chugai Pharm. Co., Ltd.*, 927 F.2d 1200, 1213, 18 USPQ2d 1016, 1027 (Fed. Cir. 1991) (noting that the *Wands* factors "are illustrative, not mandatory. What is relevant depends on the facts.").

#### The quantity of experimentation necessary

The quantity of experimentation necessary is great, on the order of several man-years, and then with little if any reasonable expectation of successfully enabling the full scope of the claims.

The amount of direction or guidance presented.

The amount of guidance provided is limited, generally prophetic, and not commensurate with the scope of the claims.

The presence or absence of working examples and breadth of claims

The specification has not been found to set forth any example, starting material or reaction condition under which the claimed method is to be practiced. Rather, the specification has been found to contain forward-looking statements as to what could or should be done.

The claims encompass the use of biochips (arrays) that are to have capture sequences immobilized thereto. Page 12, bridging to page 13, of the specification does disclose using labeled oligonucleotide that correspond to cDNA when conducting Serial Analysis of Gene Expression (SAGE). In this instance, the probes are to be 10 nucleotides in length. It is noted that there are  $4^{10}$ , or 1,048,576 possible 10-mers. The specification has not identified which of these probes are useful in the claimed method.

In the response of 28 April 2008, applicant's representative, Dr. Bieker-Brady states:

...10-mers would not be diagnostic if used in the method of present independent claims 27 and 48, but rather that the array of Brennan (U.S. Patent No. 5,474,796), which includes only 10-mers and all possible 10-mers, would not allow one to determine the presence or absence of a given, predefined pathological condition in a subject being tested. Because the Brennan array includes every permutation of 10-mer nucleic acid sequences, it would bind every species of nucleic acid molecule present in a sample containing a diverse population of nucleic acid molecules, e.g., a population of cDNA molecules prepared from nucleic acid molecules (e.g., RNAs) from nucleated blood cells of a subject, even those nucleic acid molecules not indicative of a given, predefined pathological condition. Thus, the Brennan array would be incapable of detecting whether a sample containing a diverse population of nucleic acid molecules contains differentially spliced ribonucleic acid molecules (RNAs) indicative of a given, predefined pathological condition, as is required by the method of present independent claims 27 and

48, and claims dependent therefrom, regardless of the stringency conditions used during hybridization.

It is noted with particularity that the specification teaches using these very oligonucleotides (10-mers). In accordance with claim 44, the oligonucleotides are to be immobilized on "a membrane, a glass plate, or a biochip," and in accordance with new claims 51 and 53, there are to be control molecules, which is without limit. Given such, the claims do not recite any material difference between the array to be used in the claimed method and the array disclosed by Brennan, and which applicant asserts could not function. Given such assertions, and in the absence of convincing evidence to the contrary, the claimed method cannot now be enabled by the disclosure.

On 19 May 2006 a declaration under 37 CFR 1.132 by Fabien Schweighoffer, a co-inventor named in the instant application, was filed. The declaration provides statements as to identifying specific splicing markers in the early stage of BSE in blood samples of 5 experimentally-infected cattle and 4 matching control animals. The declaration also discloses the production of a microarray; however, the declaration does not identify any nucleotide sequence for any nucleic acid bound to the support. It is further noted that the declaration does not teach the detection of any given predefined pathological condition in humans, as the claims are now limited. Further, the specification does not identify any controls, positive or negative, which are to be included in the assay (limitations of claims 51 and 53).

In accordance with new claims 50 and 52, the method is to be practiced with RNA from lymphocytes, macrophages, monocytes or dendritic cells. The specification does not describe how any one, much less each of the different cell types are to be specifically isolated, and the RNA from same be isolated and used to detect any given, predefined pathological condition.

In accordance with claim 31, one is to amplify the nucleic acids; however, the specification is silent as to what primer(s) are to be used so to amplify the target nucleic acid sequence. Indeed, the specification has not identified any target sequence in such terms that any primer could be readily identified.

The situation at hand is analogous to that in *Genentech v. Novo Nordisk A/S* 42 USPQ2d 1001. As set forth in the decision of the Court:

“ ‘[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation.’ *In re Wright* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *see also Amgen Inc. v. Chugai Pharm. Co.*, 927 F. 2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed Cir. 1991); *In re Fisher*, 427 F. 2d 833, 166 USPQ 18, 24 (CCPA 1970) (‘[T]he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.’).

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“Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. *See Brenner v. Manson*, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (stating, in context of the utility requirement, that ‘a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.’) Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention.

“It is true . . . that a specification need not disclose what is well known in the art. *See, e.g., Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the

novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research.  
(Emphasis added)

The nature of the invention

The claimed method relates generally to amplification and hybridization reactions utilizing RNAs isolated from human cells. More specifically, the claimed method relates to diagnosis of a predefined pathological condition, which causes disease in a tissue distinct from nucleated blood cells, wherein the RNA sample being analyzed is isolated from nucleated blood cells. The disease can be characterized by excessive cell proliferation.

In accordance with claims 50 and 52, the cells are lymphocytes, macrophages, monocytes or dendritic cells.

In accordance with claim 31, the RNA is subjected to amplification.

The state of the prior art and the predictability of same

US Patent 5,474,796 (Brennan) discloses an array that comprises all possible 10-mers, the same length of oligonucleotide contemplated by applicant to be used in the claimed method. Applicant, in their response of 28 April 2008 asserts that an array of all possible 10-mers cannot be used in the claimed method.

To the degree that the claims encompass the use of arrays of oligonucleotides that are longer than the 10-mers, other art-recognized problems exist. At column 40 of Jones (US Patent 5,858,671) the inherent obstacle in synthesizing oligonucleotide arrays is disclosed. As stated therein, "that even if the constituent enzymatic steps approach 100% completion, incompletely processed products can accumulate to significant levels. For example, during

oligonucleotide synthesis of a 70-mer, requiring 69 couplings, a 99% coupling efficiency results in only 50% of the generated oligonucleotides being full length ( $0.99^{69} = 0.50$ )."<sup>69</sup> In the present case, applicant's claims fairly encompass immobilized probes that would be the result of an infinite number of couplings, not just 69 as described above.

Prior, as well as post-filing art teaches of numerous problems confronting those of ordinary skill in the art. These problems have not been addressed by the instant disclosure. Absent specific guidance as to how these issues are to be overcome, one of ordinary skill in the art would be forced to trial-and-error experimentation in an effort to overcome these known issues.

Zhang et al., *Bioinformatics*, Vol. 19, No. 1, 2003, page 14, states:

It is widely recognized that the hybridization process is prone to errors and that the future of DNA sequencing by hybridization is predicated on the ability to successfully cope with such errors. However, the occurrence of hybridization errors results in the computational difficulty of the reconstruction of DNA sequencing by hybridization. The reconstruction problem of DNA sequencing by hybridization with errors is a strongly NP-hard problem. So far the problem has not been solved well.

Chan (US Patent Application Publication US 2002/0119455 A1):

[0018] In practice, Probe Up methods have been used to generate sequences of about 100 base pairs. Imperfect hybridization has led to difficulties in generating adequate sequence. Error in hybridization is amplified many times. A 1% error rate reduces the maximum length that can be sequenced by at least 10%. Thus if 1% of 65,536 oligonucleotides gave false positive hybridization signals when hybridizing to a 200-mer DNA target, 75% of the scored "hybridizations" would be false (Bains, 1997). Sequence determination would be impossible in such an instance. The conclusion is that hybridization must be extremely effective in order to generate reasonable data. Furthermore, sequencing by hybridization also encounters problems when there are repeats in sequences that are one base less than the length of the probe. When such sequences are present, multiple possible sequences are compatible with the hybridization data. (Emphasis added.)

Barany et al. (US 2007/0042419 A1), at paragraph 0036, teach in part:

For allele-specific oligonucleotide hybridization ("ASO"), the mutation must be known, hybridization and washing conditions must be known, cross-reactivity is difficult to prevent, closely-clustered sites due to interference of overlapping primers cannot undergo multiplex detection, and mutant DNA cannot be detected in less than 5% of background of normal DNA.

Choi et al. (US 2007/0042400 A1), at paragraph 0035, teach:

[0035] In conventional methods of preparing nucleic acid, polysaccharides such as starch often co-precipitate with nucleic acid. When polysaccharides co-precipitate with nucleic acid, it is difficult to manipulate nucleic acids by amplification methods, such as PCR, or by other detection methods, such as hybridization detection. Polysaccharides may also inhibit digestion with restriction endonucleases and other enzymatic manipulations.

14. It is noted that the claimed method places no lower limit on the ability to accurately and reproducibly detect any binding between polymer and unit-specific markers.
15. As evidenced above, the art is replete with known issues that directly impact the enablement of the claimed invention. A review of the instant disclosure fails to identify how these art-recognized issues are to be overcome such that the full scope of the invention can be practiced without the public having to resort to undue experimentation.
16. In view of the breadth of scope claimed, the limited guidance provided, the unpredictable nature of the art to which the claimed invention is directed, and in the absence of convincing evidence to the contrary, the claims are deemed to be non-enabled by the disclosure. For the above reasons, and in the absence of convincing evidence to the contrary, claims 27, 30-33, 44, and 47-53 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

***Conclusion***

17. Objections and/or rejections which appeared in the prior Office action and which have not been repeated hereinabove have been withdrawn.
18. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).
19. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.
20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bradley L. Sisson whose telephone number is (571) 272-0751. The examiner can normally be reached on 6:30 a.m. to 5 p.m., Monday through Thursday.
21. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, Ph.D. can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

22. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Bradley L. Sisson/  
Primary Examiner, Art Unit 1634